REMARKS

A. Claim Amendments.

By entry of the listing of claims filed herewith, claims 1-13 are cancelled and claims 14-52 are added. Claims 14-52 are pending.

Claims 14-52 correspond to claims 24-30, 32-37, 39-41, 43-57, and 74-81, as amended in an Amendment After Final filed in parent application No. 08/466,698, on February 27, 2004, which was not entered. For the Office's convenience, the following table correlates claims 14-52 with claims 24-30, 32-37, 39-41, 43-57, and 74-81, and also indicates examples of locations in the application were claims 14-52 find support.

New Claim	Corresponding Claim in Application No. 08/466,698	Support in Application as Filed
14	24	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
15	25	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
16	26	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
17	27	Original claim 3.
18	28	Original claim 5; page 5, lines 28-33.
19	29	Original claim 8.
20	30	Original claim 13; page 5, lines 28-33.
21	32	Page 6, lines 9-14.

New Claim	Corresponding Claim in Application No. 08/466,698	Support in Application as Filed
22	33	Page 6, lines 9-14.
23	34	Page 6, lines 9-14.
24	35	Page 21, lines 33-35.
25	36	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
26	37	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
27	39	Original claim 13; page 5, lines 28-33.
28	40	Original claims 3 and 5; page 5, lines 28-33.
29	41	Original claim 8.
30	43	Page 6, lines 9-14.
31	44	Page 6, lines 9-14.
32	45	Page 6, lines 9-14.
33	46	Page 6, lines 18-29.
34	47	Page 23, lines 3-12.
35	48	Page 23, lines 3-12.
36	49	Page 6, lines 18-29.
37	50	Original claim 10.
38	51	Original claim 10.
39	52	Original claim 10.
40	53	Page 23, lines 3-12.

New Claim	Corresponding Claim in Application No. 08/466,698	Support in Application as Filed
41	54	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
42	55	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
43	56	Page 23, lines 3-12.
44	57	Page 6, lines 18-29.
45	74	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
46	75	Page 23, lines 13-26.
47	76	Page 23, lines 13-26.
48	77	Page 23, lines 13-26.
49	78	Page 6, lines 18-29.
50	79	Page 1, lines 4-13; page 5, lines 8-33; original claim 1.
51	80	Page 23, lines 13-26.
52	81	Page 6, lines 18-29.

Applicants submit that no new matter enters by way of this amendment and that entry of the amendment is proper.

B. Claim Rejection Under 35 U.S.C. § 103(a) in Parent Application No. 08/466,698.

In the Final Office Action mailed May 30, 2003, in parent application No. 08/466,698, the Office maintained the rejection of claims 24-30, 32-37, 39-41, 43-57, and 74-81, under 35 U.S.C. § 103(a), as allegedly obvious over Makino in view of

Mills, Sekizaki, Nassif, and Ozenberger. (Office Action at page 2.) The Office cites Makino for disclosure of a *Shigella* comprising an inactivated *icsA* gene, inactivated by insertion of a transposon into the gene; Mills for disclosure of *Shigella* comprising an inactivated *Shiga*-toxin gene; Sekizaki for the disclosure of *Shigella* comprising an inactivated *Shiga*-toxin gene; Ozenberger for disclosure of *Shigella* comprising an inactivated enterobactin gene; and Nassif for disclosure of *Shigella* comprising an inactivated aerobactin gene. (Office Action at page 6.)

The Office acknowledges that Makino discloses inactivating an *icsA* gene of a wild strain of *Shigella* only by means of a transposon inserted into the gene, as well as the *Shigella* mutants made by this method, which necessarily comprise an inactivated *icsA* gene, inactivated only by means of a transposon inserted into the gene. The Office further acknowledges that Applicants' claim a distinct method, comprising inactivating an *icsA* gene of a wild strain of *Shigella* other than only by means of a transposon inserted into the gene, as well as the *Shigella* mutants made by this method, comprising an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene.

Nevertheless, the Office contends that one of ordinary skill would have been motivated to modify the teachings of Makino to arrive at applicants' claimed methods of producing modified *Shigella*, and applicants' claimed modified *Shigella*. The Office sees this motivation in the last paragraph of Mills, which states in reference to a mutated *Shigella* strain disclosed in Mills and distinct from applicants' claimed strains, that "[a]lthough most or all antigenic determinates involved in protective immunity are present in the attenuated *Shigella* vaccine candidate, instability of its invasive property

and the (admittedly low) potential for reversion to virulence represent possible problems." (Mills at page 121, last paragraph.) The Office asserts that Mills's statement regarding the potential for reversion to virulence in this attenuated *Shigella* vaccine candidate would be understood by one of skill in the art as teaching "that transposons, which insert themselves into a given recognition sequence[,] are also very capable of removing themselves from that site, [] thereby allowing [] the previously mutated gene to revert to normal function." (Office Action at page 5.) On the basis of this unsupported assertion, the Office concludes that one of ordinary skill would be "motivated to incorporate a further method of mutagenesis, such as deletion mutagenesis as taught by Ozenberger et al., to prevent a reversion to virulence," and thereby arrive at applicants' claims (Office Action at page 5.)

Applicants respectfully disagree with the Office's position. Applicants have filed this continuation application to further prosecute the rejected claims, with certain amendments described below, and to traverse the rejection.

C. Claims 14-52 are Nonobvious over Makino in view of Mills, Sekizaki, Nassif, and Ozenberger.

The legal concept of *prima facie* obviousness is a procedural tool to be applied during examination of patent applicants in the PTO for evaluating the nonobviousness of an applicant's claims under 35 U.S.C. § 103. *See* M.P.E.P. 2142. The Examiner bears the initial burden of establishing a *prima facie* case that the claims in a patent application are obvious. *Id.* If the Examiner does so, the burden then shifts to the applicant to present evidence and arguments rebutting the prime *facie case. Id.*

A *prima facie* case of obviousness, based on a combination of references, as relied on by the Office here, requires three elements. *Id.* "First, there must be some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings" to arrive at applicants' claims. *Id.* "Second, there must be a reasonable expectation of success." *Id.* Finally, the prior art references, when combined, must teach or suggest every limitation in applicants' claims. *Id.*

Applicants will show that none of these elements is present in the combination of references cited by the Office. Thus, the Office has not established a *prime facie* case that applicants' claims are obvious and the rejection for obviousness should not be applied to new claims 14-52.

1. Applicants' Claims.

In assessing obviousness, the dispositive determination is not "whether the differences [between the claims and the cited art] would have been obvious, but whether the claimed invention as a whole would have been obvious." M.P.E.P. 2141.02 (emphasis in original), *citing Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983). Thus, the obviousness analysis must begin with a proper construction of applicants' claims. *See National Steel Car, Ltd. V. Canadian Pacific Railway, Ltd.*, 2004 WL 190257 (Fed. Cir. (Pa.)).

Applicants amended claims are directed to methods of modifying a wild strain of an enteroinvasive *Shigella* to produce a modified strain of *Shigella* for use in making a vaccine against the wild strain of *Shigella* (claims 14-16, 37-39, and additional dependent claims), and to modified *Shigella* for use in making a vaccine against a wild strain of *Shigella* (claims 25, 26, 41, 42, 45, 50, and additional dependent claims). Claims 14 and 37 claim methods of making a modified *Shigella*, and claims 45 and 50

claim a modified *Shigella*, where the *Shigella* comprises an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene, and where the modified *Shigella* can not spread substantially within infected cells of the host and can not spread substantially from infected to uninfected cells of the host.

Claims 15 and 80 claim methods of making a modified *Shigella*, and claims 25 and 41 claim a modified *Shigella*, where the *Shigella* comprises an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene, and an inactivated aerobactin or enterochelin gene, inactivated other than only by means of a transposon inserted into the gene. In each claim, the modified *Shigella* can not spread substantially within infected cells of the host, can not spread substantially from infected to uninfected cells of the host, and can not substantially invade cells of the host.

Claims 16 and 81 claim methods of making a modified *Shigella*, and claims 26 and 42 claim a modified *Shigella*, where the *Shigella* comprises an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene, an inactivated aerobactin or enterochelin gene, inactivated other than only by means of a transposon inserted into the gene, and an inactivated Shiga-toxin gene, inactivated other than only by means of a transposon inserted into the gene. In each claim, the modified *Shigella* can not spread substantially within infected cells of the host, can not spread substantially from infected to uninfected cells of the host, can not substantially invade cells of the host, and can not produce toxins that kill a substantial number of host cells.

Thus, applicants' claims recite specific phenotypic characteristics of the claimed modified *Shigella*, for use in making a vaccine against a wild strain of *Shigella*, which are not present in the starting wild strain of *Shigella*.

As described above, applicants' method claims all comprise inactivating an *icsA* gene of a wild strain of *Shigella* other than only by means of a transposon inserted into the gene. Similarly, applicants' claimed *Shigella* all comprise an inactivated *icsA* gene, inactivated other than only by means of a transposon inserted into the gene.

2. Neither Mills Nor Any Other Cited Reference Provides a Suggestion or Motivation to Modify Makino to Arrive at Applicants Claimed Invention, Taken as a Whole.

a. The *icsA* Phenotype Disclosed in Makino Does Not Provide a Suggestion or Motivation to Make an *icsA* Mutant *Shigella* for Use as a Vaccine.

As described above, Makino discloses inactivating an *icsA* gene of a wild strain of *Shigella* only by means of a transposon inserted into the gene, as well as the *Shigella* mutants made by this method, which necessarily comprise an inactivated *icsA* gene, inactivated only by means of a transposon inserted into the gene. These mutants are distinct from applicants' claimed methods and modified strains, which all require inactivating an *icsA* gene of a wild strain of *Shigella* other than only by means of a transposon inserted into the gene. The Office sees a motivation to modify the disclosure of Makino to arrive at applicants' claims in Mills. A proper reading of Makino shows that this is simply not so.

Applicants are submitting herewith, as Exhibit I, the Declaration of Jean-Michel Alonso, M.D., Ph.D., Under 37 C.F.R. § 1.132 ("Alonso Declaration" or "Exhibit I")[1]. The Alonso Declaration explains the phenotypic characterization of *virG* mutant *S. flexneri* described in Makino. (Exhibit I at 11.) (Because *virG* and *icsA* are different names for the same gene, and because the '698 application and the pending claims refer to the gene as *icsA*, the Alonso Declaration, like this Response, refers to the gene as *icsA*, including in reference to Makino.) In particular, the Alonso Declaration describes and interprets the significance of the phenotypic characterization provided by Makino to the suitability of a modified *Shigella* comprising an inactivated *icsA* for use in making a vaccine against a wild strain of *Shigella*, from the perspective of one of skill in the art as of July 15, 1988. (Exhibit 1 at 11.)

According to Makino, *Shigella* comprising an inactivated *icsA* gene can invade host cells and multiply within host cells, but are then extinguished before they can spread and infect adjacent cells. (Exhibit I at 12.) Makino also states that *Shigella* comprising an inactivated *icsA* gene lack active movement, show a tendency to localize within the cytoplasm, are gradually converted to a spherical morphology, and are finally extinguished from the epithelia. (Exhibit I at 13.) These disclosures of Makino show

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1. The Alonso Declaration was originally filed with an Amendment After Final filed in parent application No. 08/466,698, on February 27, 2004. Thus, the Alonso Declaration references the '698 application and refers to the claims, as amended, in the Amendment After Final filed on February 27, 2004. The table presented herein correlates claims 24-30, 32-37, 39-41, 43-57, and 74-81 as amended in the Amendment After Final to claims 14-52 in the instant application. Thus, all of the statements made in the Alonso Declaration apply equally to the pending claims in the instant application.

that *Shigella* comprising an inactivated *icsA* gene retain the ability to invade host cells, but have lost the ability to spread from infected to uninfected host cells, and have also lost the ability to spread within infected host cells. (Exhibit I at 12 and 13.)

In evaluating Makino, the relevant inquiry is how Makino would have been understood by one of skill in the art as of July 15, 1988, the filing date of applicants' priority European Patent Application Serial No. 88 401 842.5. *See* M.P.E.P. 2141.01 (III), *citing W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir 1983), *cert. denied*, 469 U.S. 851 (1984). At that time, one of skill in the art knew that making a modified *Shigella* strain for use in a vaccine "would require modifying a wild *Shigella* strain by mutating one or more genes required for pathogenicity of the wild strain, to create a modified strain that will invade and multiply in a host, but, unlike the corresponding wild strain, will not cause a disease pathology." (Exhibit I at 15.) Critically, "[i]t was appreciated that, while attenuation of the strain is critical to render the strain non pathogenic, it is imperative that the strain retain some ability to invade, multiply, and spread within an inoculated host, so that the strain elicits a significant enough immune response to confer immunity to the wild strain to the host." (Exhibit I at 15.)

Judged from this perspective, the teachings of Makino would not lead one of skill in the art to expect that a modified *Shigella* strain comprising an inactivated *icsA* gene would be useful as a modified strain for making a vaccine against the wild *Shigella* strain. (Exhibit I at 16.) This is so even though Makino states that modified *Shigella* strains comprising an inactivated *icsA* gene "may be a plausible candidate for a live vaccine against bacillary dysentery." (Makino at page 554, left col.) This assertion is

clearly contrary to the description of the modified *Shigella* strain comprising an inactivated *icsA* gene provided by Makino—taking the reference as a whole and focusing on the teachings therein. (Exhibit I at 17.) According to Makino, the modified strain is unable to survive in cells or tissues and does not spread within or between cells. (Exhibit I at 17.) Thus, the strain would not be expected to elicit a robust immune response and would not have been viewed by one of skill, as of July 15, 1988, as effective for making a vaccine.

Once the teachings of Makino are properly understood, it is clear that "based on the disclosure in Makino, and based on what was known about the molecular genetics of pathogenic bacteria as of July 15, 1988, [one of skill in the art] would not have been motivated to include an inactivated *icsA* gene in a modified *Shigella* strain for use in making a vaccine." (Exhibit I at 18.)

b. There is no Motivation to Combine Mills's Teachings, Regarding How to Modify a *Shigella* Strain For Use in Making a Vaccine, with Makino's Teachings, that *icsA* is Not Suitable for use in a Vaccine.

Mills reviews attempts to modify *Shigella* to make vaccine strains. In this regard, Mills observes that "[a]lthough most or all antigenic determinates involved in protective immunity are present in the attenuated *Shigella* vaccine candidate, instability of its invasive property and the (admittedly low) potential for reversion to virulence represent possible problems." (Mills at page 121, last paragraph.) The Office grasps onto this statement and characterizes it as providing motivation to one of skill "to incorporate a further method of mutagenesis, such as deletion mutagenesis as taught by Ozenberger et al., to prevent a reversion to virulence," into the *icsA* mutants of Makino to thereby arrive at applicants' claims (Office Action at page 5.) This position is untenable in view

of a proper understanding of Makino from the perspective of one of skill in the art as of July 15, 1988, as described above.

Even assuming, for the sake of argument only, that Mills did provide a motivation to use a method of mutagenesis other than only by means of a transposon inserted into a gene when modifying a wild strain of *Shigella* to make a modified strain for use in making a vaccine, as recited in applicants' claims, one of skill would clearly have had no motivation to apply this mutagenesis method to the *icsA* gene in view of the teachings of Makino, as described above. Thus, Mills provides no motivation to modify Makino to arrive at applicants' claims. Therefore, the Office has failed to provide a motivation to modify Makino to arrive at applicants' claims and the rejection for obviousness should be withdrawn for at least this reason.

3. One of Ordinary Skill in the Art Would Not Have Expected Success in Modifying Makino Based on Mills.

Applicants claims recite methods of modifying a wild strain of an enteroinvasive *Shigella* to produce a modified strain of *Shigella* for use in making a vaccine against the wild strain of *Shigella*, and modified *Shigella* for use in making a vaccine against a wild strain of *Shigella*. Based on the disclosure in Makino, and based on what was known in the art as of July 15, 1988, one of skill in the art would have assumed that inclusion of an inactivated *icsA* gene in a *Shigella* strain for use in making a vaccine would have rendered it ineffective in making a vaccine against a wild strain of *Shigella*. (Exhibit I at 18.) Nothing in Mills would have changed this expectation of failure. An expectation of failure is the antithesis of an expectation of success. As one of skill in the art would not have expected success in modifying Makino based on Mills, applicants' claims are

necessarily nonobvious over the cited references and the rejection for obviousness should be withdrawn for at least this reason as well.

4. The Cited References Do Not Disclose Every Limitation of Applicants' Claims, Alone or in Combination.

Applicants are submitting herewith, as Exhibit II, the Declaration of Stewart Thomas Cole, Ph.D., Under 37 C.F.R. § 1.132 ("Cole Declaration" or "Exhibit II")[2]. The Cole Declaration explains the significance of certain terms that appear in the amended claims to describe the phenotype of the modified *Shigella*. (Exhibit II at 10.)

As described in the Cole Declaration, claim 14 recites "[a] method for modifying a wild strain of an enteroinvasive *Shigella* to produce a modified strain of *Shigella* that can not spread substantially within infected cells of a host and can not spread substantially from infected to uninfected cells of the host, for use in making a vaccine against the wild strain of *Shigella*. . . ." (Exhibit II at 14.) This language means that "the ability of the strain to spread within infected host cells, and from infected to uninfected host cells, is substantially reduced. However, the ability of the strain to spread within infected host cells, and from infected to uninfected host cells, is clearly not abolished. If it were, the modified strain would not be useful to make a vaccine against the wild strain of *Shigella*." (Exhibit II at 14.)

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2. Like the Alonso Declaration, the Cole Declaration was originally filed with an Amendment After Final filed in parent application No. 08/466,698, on February 27, 2004. Thus, the Alonso Declaration references the '698 application and refers to the claims, as amended, in the Amendment After Final filed on February 27, 2004. The table presented herein correlates claims 24-30, 32-37, 39-41, 43-57, and 74-81 as amended in the Amendment After Final to claims 14-52 in the instant application. Thus, all of the statements made in the Alonso Declaration apply equally to the pending claims in the instant application.

Similarly to proposed claim 14, each of proposed claims 25, 26, 41, 42, 45, and 50 recites a modified *Shigella* that "can not spread substantially within infected cells of a host and can not spread substantially from infected to uninfected cells of the host." Each of these claims recites "[a] modified *Shigella* for use in making a vaccine against a wild strain of *Shigella*." In each claim, this language means "that the ability of the modified strain to spread within infected host cells, and from infected to uninfected host cells, is substantially reduced. However, the ability of the strain to spread within infected host cells, and from infected to uninfected host cells, is clearly not abolished. If it were, the modified strain would not be useful to make a vaccine against the wild strain of *Shigella*." (Exhibit II at 15.)

These limitations in applicants' claims regarding the phenotype of the modified *Shigella* are not taught or suggested in Makino. None of the other cited references remedy this deficiency of Makino. Thus, the cited references, taken as a whole, do not disclose every limitation of applicants' claims. Therefore, applicants' claims are nonobvious over the cited references and the rejection for obviousness should be withdrawn for at least this reason as well.

To the extent the Office may wish to rely on allegedly inherent features of the Makino disclosure, applicants note it is well established that, "[t]hat which may be inherent is not necessarily known." *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), *quoting In re Sporman*, 363 F.2d 444, 448, 53 C.C.P.A. 1375, 1380, 150 U.S.P.Q. 449, 452 (1966). Consequently, because "[o]bviousness cannot be predicated on what is unknown," *Id.*, it is improper to base a rejection for obviousness on the inherent disclosure of a prior art reference. *See* MPEP 2141.02 ("Obviousness cannot be

predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established.").

D. Conclusion

Applicants respectfully request entry of this Preliminary Amendment and timely allowance of the pending claims 14-52.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: August 17, 2004

By: _____
Kenneth J. Meyers
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Attachments: **Exhibit 1 (including Exhibits A-F thereto)**
Exhibit 2 (including Exhibits A-F thereto)